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RESPONSE TO COMMENT ON PONGRAC BARLOVIC ET AL.

The Association of Severe Diabetic Retinopathy With Cardiovascular Outcomes in Long-standing Type 1 Diabetes: A Longitudinal Follow-up. Diabetes Care 2018;41:2487–2494

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We are thankful for the response from Camoin et al. (1) to our article (2) showing the association of severe diabetic retinopathy (SDR) with cardiovascular disease, including peripheral artery disease, in long-standing type 1 diabetes. Importantly, the association was present even in the absence of DKD, a well-established risk factor for cardiovascular events and premature mortality (3). Results from the French cohort of patients with type 1 diabetes further strengthen the importance of SDR as a risk factor for lower-extremity ischemia, foot ulcers, and amputations. In their cohort ($n = 204$) they were able to show an association between SDR and foot ulcers after adjustment for the presence of DKD and other cardiovascular risk factors, even with shorter diabetes duration (21 ± 13 years) and shorter follow-up (7 years). Moreover, they propose that the association is mediated through peripheral neuropathy, since it was more prevalent in their patients with SDR. However, they do not present data on the association between peripheral neuropathy and cardiovascular disease, myocardial infarction, and stroke.

Similarly, data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study reported an independent association between cardiac autonomic neuropathy and cardiovascular events, also after adjustment for albuminuria, but not specifically between peripheral neuropathy and cardiovascular events (4). In addition, data from the Joslin Diabetes Center's cohort of patients with very long type 1 diabetes duration also do not point to the association of peripheral neuropathy and cardiovascular events (5). Interestingly, however, recently published data from the Canadian Study of Longevity in Type 1 Diabetes cohort ($n = 69$) show that coronary artery calcium scores were higher in patients with sensory polyneuropathy and diabetic retinopathy, but not with DKD or autonomic neuropathy (6). However, since coronary calcification scores cannot differentiate between stable and vulnerable plaques, they could not reliably predict incident acute cardiovascular events.

Associations of SDR or peripheral neuropathy with cardiovascular disease in the absence of DKD are important, as they suggest the need for continued vigilance to reduce cardiovascular risk even in the absence of DKD and in long-standing diabetes (2). Since both microvascular and macrovascular disease share similar risk factors in long-standing diabetes (4), the independent association of isolated sensory polyneuropathy with cardiovascular disease would be of no surprise, but it has not yet been shown. Until more longitudinal and mechanistic data become available, SDR should be regarded as an independent risk factor for critical limb ischemia and foot ulcers, as well as for other types of cardiovascular disease. Therefore, regular diabetic foot screening tests in this population are of the utmost importance.

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